

Thimerosal and the Relevance of Patch-Test Reactions in Children

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Thimerosal ($C_9H_9HgNaO_2S$) is a mercuric derivative of thiosalicylic acid that goes by many names. It has been used as a disinfectant (eg, Merthiolate) and as a preservative in some vaccines, cosmetics, tattoo inks, eye drops, and contact lens solutions. It remains one of the least likely chemicals to cause contact allergy and for this reason has been removed from many standard screening series. Positive patch-test reactions (demonstrating sensitization) may still be seen (especially in older children); however, these reactions are not clinically relevant and are expected to be fewer, reflecting changes in current vaccine formulations.

Thimerosal ($C_9H_9HgNaO_2S$) is a mercuric derivative of thiosalicylic acid that goes by many names (Table 1). It has been used as a disinfectant (under the trade name Merthiolate, formerly manufactured by Eli Lilly and Company, Indianapolis, IN) and as a preservative in some vaccines, cosmetics, tattoo inks, eye drops, and contact lens solutions. Because of the way it is used, most clinically relevant allergic reactions to thimerosal occur with cosmetics use or after contact with ophthalmic preparations, which results in a periorbital dermatitis.¹ Likewise, thimerosal allergy is most commonly found among women, health care workers, and cooks owing to increased cosmetic use in women and to vaccination of health care workers and cooks.²

It is important to note that, to confirm sensitization, a closed patch test should be performed, in which an allergen is applied to the skin of the back or to the inner aspect of the upper arm for 24 to 48 hours. The patches are then removed, and the patient returns for a third visit at 72 to 120 hours, when the patch test is evaluated for erythema, induration, papulovesiculation, and/or bullae. A reaction will occur if there has been prior exposure to the chemical and immunologic recognition occurs.

To confirm contact allergy, the sensitization must be relevant to the current clinical dermatitis being investigated. Currently, there is one Food and Drug

Administration–indicated commercially available patch-test screening tool, the T.R.U.E. Test (Mekos Laboratories A/S, Hillerød, Denmark), for testing in adults (the current indication does not include persons younger than 18 years). Alternatively, many patch-test referral centers perform extended series testing in which allergens are prepared and tailored to the individual's history of current dermatitis. In the United States, the North American Contact Dermatitis Group (NACDG), a consortium of these referral centers, pools their data and publishes their findings periodically.

In the studies done in 2000 by the NACDG, thimerosal ranked as the fifth most common sensitizer and had a positive patch-test reaction rate of 10.2%.³ A more recent meta-analysis of 15 years of T.R.U.E. Test data found thimerosal to be the second most common allergen in the test (the first was nickel), with a positive patch-test reaction rate of 5.0%.⁴ In 2002, thimerosal was designated Allergen of the Year by the American Contact Dermatitis Society because it demonstrated a low clinical relevance of only 7.2% despite its high prevalence as a sensitizer.⁵ Because of this, it was determined that, of the 65 allergens tested by the NACDG, thimerosal was one of the least

Table 1. Other Names for Thimerosal

Merthiolate (Eli Lilly and Co. Indianapolis, IN)
Mercurochrome
Merfamin
Thiomersal
Ethylmercurithiosalicylate sodium
Mercural
Merphol
Septicol
Thimersalate

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likely chemicals to cause contact allergy,⁶ a finding that has also been confirmed in pediatric populations.⁷ Following this, the NACDG and other tertiary care centers in the United States removed thimerosal from their standard screening series. Thimerosal remains on the T.R.U.E. Test panel because of its continued relevance in Russia and Japan. It may, however, be replaced on the US panel in the near future (Kim Sullivan, Allerderm, April 2008).

For this reason, physicians who choose to use the T.R.U.E. Test panel may continue to see adults and older children with positive patch-test reactions (sensitization) to thimerosal that have no clinical relevance to the problem at hand. That being said, these rates are expected to wane as manufacturers increasingly choose to use alternative preservatives in vaccine preparations.⁸ Also, the question of the safety of continuing to use thimerosal-containing vaccinations in sensitized persons has often arisen. Pivotal studies performed to address this issue showed that vaccinations containing thimerosal were safe to administer even in sensitized individuals.⁹ Audicana and colleagues conducted a trial in which individuals sensitive to mercury derivatives were challenged with intramuscular injections of thimerosal in increasing concentrations. No cutaneous reactions were observed in 91% of the patients, and the remaining 9% had only mild reactions characterized by local induration and micropapules.¹⁰ Furthermore, a retrospective case-control study by Cox and Forsyth showed that patients with positive patch-test reactions to thimerosal did not have significantly more vaccination reactions than did patch-test-negative controls.¹¹

In 1997, the Food and Drug Administration (FDA) mandated a review of all mercury-containing food and drugs and issued the following statement:

Our review revealed no evidence of harm caused by doses of thimerosal found in vaccines, except for local hypersensitivity reactions. At the time of our review, vaccines containing thimerosal as a preservative could expose infants to cumulative mercury at levels that exceed EPA [Environmental Protection Agency] recommendations during the first 6 months of life. The clinical significance of this conclusion is not currently known; EPA guidelines contain as much as a 10-fold safety factor and such guidelines are meant to be starting points for the evaluation of mercury exposure. However, reducing exposure to thimerosal from vaccines is merited given the goal of reducing human exposure to mercury from all sources, the

feasibility of removing thimerosal as a vaccine preservative, and the desirability of ensuring public confidence in the safety of vaccines.¹²

Despite the lack of convincing evidence for thimerosal toxicity, the US Public Health Service and the American Academy of Pediatrics advised that all thimerosal should be removed from vaccines as a preventative measure and to increase public confidence in vaccination programs¹³ (Table 2). This recommended removal spurred controversy over a link between thimerosal-containing vaccines and autism in infants and children. The evidence for a connection between the two was a mixture of in vitro tests showing adverse effects of ethylmercury on cultured cells¹⁴ and epidemiologic studies examining correlations between thimerosal and autism.¹⁵ However, although the consensus of the scientific community (including the FDA,¹⁵ the Centers for Disease Control,¹⁶ and the World Health Organization¹⁷) rejects the hypothesis that exposure to thimerosal causes or contributes to autism or other neurologic disorders, thimerosal has been removed from all vaccines routinely recommended for children 6 years of age or younger, with the exception of inactivated influenza vaccine.¹⁸

Table 2. Vaccines with and without Thimerosal

<i>Vaccines with Thimerosal</i>	<i>Vaccines without Thimerosal</i>
Influenza	MMR
Japanese encephalitis	Pneumococcal
Some hepatitis B	Rabies
DTaP (Tripedia*)	DTaP (Infanrix, [†] Daptacel*)
	Smallpox
	Varicella
	Hib
	Polio (Salk)

DTaP = diphtheria and tetanus toxoids and acellular pertussis; Hib = *Haemophilus influenza* type b; MMR = measles-mumps-rubella.

*Sanofi Pasteur, Lyon, France.

[†]GlaxoSmithKline, Middlesex, UK.

References

- Herbst RA, Uter W, Pirker C, et al. Allergic and non-allergic periorbital dermatitis: patch test results of the Information Network of the Departments of Dermatology during a 5-year period. *Contact Dermatitis* 2004;51:13–9.
- Suneja T, Belsito DV. Thimerosal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001;45:23–7.
- Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1998–2000. *Am J Contact Dermat* 2003;14:59–62.

4. Krob HA, Fleischer AB, D'Agostino R, et al. Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. test data. *J Am Acad Dermatol* 2004;51:346–53.
5. Belsito DV. Thimerosal: contact (non)allergen of the year. *Am J Contact Dermat* 2002;13:1–2.
6. Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998;36:911–8.
7. Jacob SE, Brod BA, Crawford GH. Clinically relevant patch test reactions in children—a United States based study. *Pediatric Dermatology Journal* [In press]
8. Centers for Disease Control. Thimerosal in vaccines. May 12, 2008. Available at: <http://www.fda.gov/cber/vaccine/thimerosal.htm> (accessed May 25, 2008).
9. Aberer W. Vaccination despite thimerosal sensitivity. *Contact Dermatitis* 1991;24:6–10.
10. Audicana MT, Munoz D, del Pozo MD, et al. Allergic contact dermatitis from mercury antiseptics and derivatives: study protocol of tolerance to intramuscular injections of thimerosal. *Am J Contact Dermat* 2002;13:3–9.
11. Cox NH, Forsyth A. Thimerosal allergy and vaccination reactions. *Contact Dermatitis* 1988;18:229–33.
12. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 2001;107:1147–54.
13. Baker JP. Mercury, vaccines, and autism: one controversy, three histories. *Am J Public Health* 2008;98:244–53.
14. Ames SJ, Slikker W III, Melnyk S, et al. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. *Neurotoxicology* 2005;26:1–8.
15. Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. *Neuro Endocrinol Lett* 2006;27:401–13.
16. Centers for Disease Control. Mercury and vaccines (thimerosal). January 8, 2007. Available at: <http://www.cdc.gov/od/science/iso/concerns/thimerosal.htm> (accessed April 1, 2008).
17. World Health Organization. Thimerosal vaccines: questions and answers. July 2006. Available at: http://www.who.int/vaccine_safety/topics/thiomersal/questions/en/ (accessed April 1, 2008).
18. Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. Thimerosal in vaccines, September 6, 2007; Available at: <http://www.fda.gov/cber/vaccine/thimerosal.htm> (accessed April 1, 2008).